

EXHIBIT D



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The Special Risks of Pharmacy Compounding



Pharmacy compounding is an age-old practice in which pharmacists combine, mix, or alter ingredients to create unique medications that meet specific needs of individual patients.

It's also a practice that is under FDA scrutiny—mainly because of instances where compounded drugs have endangered public health.

"In its traditional form, pharmacy compounding is a vital service that helps many people, including those who are allergic to inactive ingredients in FDA-approved medicines, and others who need medications that are not available commercially," says Kathleen Anderson, Pharm.D, Deputy Director of the Division of New Drugs and Labeling Compliance in FDA's Center for Drug Evaluation and Research (CDER).

Compounded medications are also prescribed for children who may be unable to swallow pills, need diluted dosages of a drug made for adults, or are simply unwilling to take bad-tasting medicine.

"But consumers need to be aware

that compounded drugs are not FDA-approved," Anderson says. "This means that FDA has not verified their safety and effectiveness."

Steve Silverman, Assistant Director of CDER's Office of Compliance, says that poor practices on the part of drug compounders can result in contamination or in products that don't possess the strength, quality, and purity required. "And because patients who use these drugs may have serious underlying health conditions," he says, "these flawed methods pose special risks."

Unlike commercial drug manufacturers, pharmacies aren't required to report adverse events associated with compounded drugs. "FDA learns of these through voluntary reporting, the media, and other sources," says Silverman.

The Agency knows of more than

200 adverse events involving 71 compounded products since 1990. Some of these instances had devastating repercussions.

- Three patients died of infections stemming from contaminated compounded solutions that are used to paralyze the heart during open-heart surgery. FDA issued a warning letter in March 2006 to the firm that compounded the solutions.
- Two patients at a Washington, D.C., Veterans Affairs hospital were blinded, and several others had their eyesight damaged, by a compounded product used in cataract surgery. The product was contaminated with bacteria. In August 2005, FDA announced a nationwide recall of this Trypan Blue Ophthalmic Solution. Contaminated solution had been



distributed to hospitals and clinics in eight states.

- In March 2005, FDA issued a nationwide alert concerning a contaminated, compounded magnesium sulfate solution that caused five cases of bacterial infections in a New Jersey hospital. A South Dakota patient treated with the product developed sepsis and died.

A Troubling Trend

The emergence over the past decade of firms with pharmacy licenses making and distributing unapproved new drugs in a way that's clearly outside the bounds of traditional pharmacy is of great concern to FDA.

"The methods of these companies seem far more consistent with those of drug manufacturers than with those of retail pharmacies," says Silverman. "Some firms make large amounts of compounded drugs that are copies or near copies of FDA-approved, commercially available drugs. Other firms sell to physicians and patients with whom they have only a remote professional relationship."

FDA highlighted these concerns in August 2006, when it warned three firms to stop manufacturing and distributing thousands of doses of compounded, unapproved inhalation drugs nationwide.

Inhalation drugs are used to treat diseases including asthma, emphysema, bronchitis, and cystic fibrosis. "These are potentially life-threatening conditions for which numerous FDA-approved drugs are available," says Silverman. "Compounded inhalation drugs may be distributed to patients in multiple states, and patients and their doctors may not understand that they are receiving compounded products."

Enforcement

"FDA historically hasn't directed enforcement against pharmacies engaged in traditional compound-

ing," says Anderson. "Rather, we've focused on establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new-drug, adulteration, or misbranding provisions of the Federal Food, Drug, and Cosmetic Act."

FDA counts compounded drugs among the new drugs that are covered under the Act. "We consider them new because they're not generally recognized among experts as safe and effective," says Anderson.

She adds that FDA recognizes that states have a central role in regulating pharmacy compounding. "We refer complaints to the states, support them when they request it, and cooperate in investigations and follow-up actions. But there are cases when states are unable to act, and we proceed without them," Anderson says.

Red Flags

In a May 29, 2002, Compliance Policy Guide devoted to human pharmacy compounding, FDA identifies factors that it considers in deciding upon enforcement action. These factors include instances where pharmacists are:

- compounding drug products that have been pulled from the market because they were found to be unsafe or ineffective.
- compounding drugs that are essentially copies of a commercially available drug product.
- compounding drugs in advance of receiving prescriptions, except in very limited quantities relating to the amounts of drugs previously compounded based on valid prescriptions.
- compounding finished drugs from bulk active ingredients that aren't components of FDA-approved drugs, without an FDA-sanctioned, investigational new-

drug application.

- receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
- failing to conform to applicable state law regulating the practice of pharmacy.

What You Can Do

What can consumers do to protect themselves against inappropriate drug-compounding practices? Ilisa Bernstein, Pharm.D, J.D., Director of Pharmacy Affairs in FDA's Office of the Commissioner, offers these tips:

- Ask your doctor if an FDA-approved drug is available and appropriate for your treatment.
- Check with the pharmacist to see if he or she is familiar with compounding the product in your prescription.
- Get information from your doctor or pharmacist about proper use and storage of the compounded product.
- If you receive a compounded product, ask the pharmacist if the doctor asked for it to be compounded.
- If you experience any problems or adverse events, contact your doctor or pharmacist immediately and stop using the product.
- Report any adverse events experienced while using the product to FDA's MedWatch program at <http://www.fda.gov/medwatch/> 